REMARKS

I. Status of the Claims

Claims 1-9, 12 and 14-18 are pending in the application, claims 10, 11 and 13 having been canceled. Claims 1-9 and 12 stand withdrawn. Claims 14-20 are under examination and stand rejected for alleged lack of enablement, claims 14 and 19 are rejected for alleged anticipation, and claims 14,16 and 18-20 stand rejected for alleged obviousness. The specific grounds for rejection, and applicants' response thereto, are set out in detail below.

II. Rejection Under 35 U.S.C. §112, First Paragraph

Claims 14-20 stand rejected as lacking enablement for the full scope of the claimed subject matter. According to the examiner, the claims remain too broad in claiming treatment of cancers beyond malignant melanoma, and in the use of GnRH antagonists. Each of these issues is addressed below.

A. Non-melanoma Cancers

At the outset, applicants are providing a copy of the declaration that was said to be missing from the prior response. As applicants' postcard that accompanied the response indicated that the declaration had been sent, applicants request consideration of the content of the declaration as now resubmitted.

The attached declaration puts forth additional evidence showing the distribution of GnRH receptors on various cancers. In this regard, applicants note that the claims are not nearly as broad as argued by the examiner – "any type of tumor" is not claimed. To the contrary, the claims recite decreasing the replication of a GnRH-receptor positive tumor, and further reciting a

list of several cancer. This is a very ***specific*** type of tumor for which GnRH analog therapy has already been implicated. Applicants have merely extended the list of cancers that can be treated by ascertaining the expression of GnRH receptors by such cancers.

The examiner attempts to undercut the significance of the academic reports provided by applicants on the ground that they address cancers not now claimed. However, the point of these submissions is to show that where cancer cells express the GnRH receptor, they are in general susceptible to treatment with GnRH agonists and antagonists. In light of these showings, the examiner is compelled to come forward with reasons to find that applicants' data on GnRH receptor distribution is not a sufficient to make out a *prima facie* case of enablement.

Next, the examiner attacks the Groeninghen *et al.* paper based on certain allegedly equivocal statements therein. However, the fact that Groeninghen *et al.* might have qualified their conclusions is irrelevant, given the constraints of academic publication. The question instead is whether one of skill in the art, viewing the ***totality*** of the data now before the examiner, including numerous papers, the attached declaration and the instant specification, would find it more reasonable than not that GnRH-receptor positive cancers could be treated by some form of GnRH agonist or antagonist therapy. The examiner has not established a credible argument that the skilled artisan would ***not*** find such an endeavor reasonable, and it is the PTO's burden to do so. *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367 , 370 (CCPA 1971) ("...[I]t is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise, there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure.").

B. GnRH Antagonists

The examiner has identified Moretti *et al.* as teaching that the inhibitory effect of LHRH agonists can be counteracted by LHRH antagonists. However, the examiner is misunderstanding the significance of the reference's disclosure regarding antagonists. As acknowledged by the examiner, the purpose of this experiment was to determine the specific nature of the LHRH agonist activity, and the only way to do that was to block signaling through the cognate receptor by using an LHRH antagonist. It is ***critical*** to note that Moretti *et al.* carefully selected ***non-inhibitory*** concentrations of the antagonist for their experiment:

> ...In preliminary experiments, the activity of ANT was evaluated. Figure 5A shows that the antagonist did not affect the proliferation of the cells, when given at the doses of 10^{-11}-10^{-7} M. The compound reduced slightly, but not significantly, the growth of BLM cells at the dose of 10^{-6} M. For subsequent experiments, the dose of 10^{-7} M was then selected....

Moretti *et al.*, p. 3794. Thus, the ***real*** suggestion by Moretti *et al.* is that using doses higher than 10^{-7} M of the antagonist could very well have proved inhibitory. This is supported by the Pinski *et al.* and Vincze *et al.* references that show both agonists and antagonists can inhibit cancer cell proliferation. Thus, it is simply not true, as argued by the examiner, that the art only supports the use of agonists of GnRH.

C. Summary

The examiner's summary of the rejection, set forth at page 9 of the action, provides an excellent recap of why the rejection is improper. First, it is argued that the literature only supports treating melanoma with agonists. While arguably true, there is data and scientific

reasoning of record explaining why the use of GnRH antagonists should not be doubted (and Moretti cannot undercut this position for the reasons given). Second, it is argued that the literature on reproductive cancers only supports unclaimed cancers. That is wrong – these cancers, like those now claimed, have GnRH receptors. This provides an excellent and unchallenged rationale in ***favor*** of treating the cancers recited in applicants' claims. Third it is argued that if the teachings of the prior art supported the claims, they would render it obvious. That also is untrue because the prior art on reproductive cancers could not have established, as have applicants, that the cancers applicants are claiming express GnRH receptors. And fourth, though the literature may have suggested additional research was required to fully exploit GnRH receptor-directed therapies, that same literature was without the benefit of applicants' data. In sum, every concern stated by the examiner has been effectively rebutted by this response. As such, applicants respectfully request reconsideration and withdrawal of the rejection.

III. Rejection Under 35 U.S.C. §102

Claims 14 and 19 stand rejected under §102 as allegedly anticipated by Laue *et al.* According to the examiner, optic gliomas in six patients treated with an LHRH analog would have been "inherently" treated by the administered agent. Applicants traverse.

The standards under which the PTO is permitted to advance an "inherency" rejection are ***extremely*** high. The fact that a certain result or characteristic ***may*** occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. *In re Rijckaert*, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993) (reversed rejection because inherency was based on what would result due to optimization of conditions, not what was necessarily present in the prior art); *In re Oelrich*, 666 F.2d 578, 581-82, 212 USPQ 323, 326

(CCPA 1981). Instead, "[t]o establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.'" *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999) (citations omitted) (The claims were drawn to a disposable diaper having three fastening elements. The reference disclosed two fastening elements that could perform the same function as the three fastening elements in the claims. The court construed the claims to require three separate elements and held that the reference did not disclose a separate third fastening element, either expressly or inherently.).

"In relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic ***necessarily*** flows from the teachings of the applied prior art."" *Ex parte Levy,* 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990) (emphasis in original) (Applicant's invention was directed to a biaxially oriented, flexible dilation catheter balloon (a tube which expands upon inflation) used, for example, in clearing the blood vessels of heart patients). The examiner applied a U.S. patent to Schjeldahl which disclosed injection molding a tubular preform and then injecting air into the preform to expand it against a mold (blow molding). The reference did not directly state that the end product balloon was ***biaxially oriented***. It did disclose that the balloon was "formed from a thin flexible inelastic, high tensile strength, biaxially oriented synthetic plastic material." *Id.* at 1462 (emphasis in original). The examiner argued that Schjeldahl's balloon was inherently biaxially oriented. The Board reversed on the basis that the examiner did

not provide objective evidence or cogent technical reasoning to support the conclusion of inherency.).

Here, the patients had "optic gliomas," but nothing more about this condition was reported. Similarly, there is no mention of the effects of the LHRH analog therapy on these lesions. Thus, in order for the examiner to advance this rejection, it must be that the treatment ***necessarily*** resulted in an impact on the optic gliomas. However, it is entirely unclear whether these gliomas were (a) already drug resistant, (b) generally insulated from treatments given in the route(s) as reported, or (c) insufficiently vascularized to receive LHRH analogs regardless of route. With regard to (b), applicants note that the examiner asserts that the drug was administered via an intravenous route, as discussed in the "Protocol" section on page 1097, but that same page, under "Patients and Methods" indicates that a subcutaneous route was used. Given these unanswered questions, there is no question that this rejection fails to live up to the high standards set forth above. As such, applicants submit that the rejection is improper, and reconsideration and withdrawal of the rejection are respectfully requested.

IV. Rejection Under 35 U.S.C. §103

Claims 14, 16 and 18-20 stand rejected under §103 as allegedly rendered obvious over He *et al.* By the examiner's own admission, He *et al.* teaches only a screening method, whereas t the present claims are directed to therapeutic methods. Nonetheless, the examiner finds the reference sufficient to render obvious applicants' claims. Applicants traverse.

From a factual standpoint, the rejection simply does not stand up. Though He *et al.* apparently report that the "cell growth rate" of certain melanoma cell lines was "decreased," they also show that H^3-thymidine and -uridine incorporation went ***up***, which the skilled artisan would

recognize as an ***increase*** in a cell's metabolic activity. Moreover, ***no effects*** on cell cycle were seen. At best, these studies present very ambiguous conclusions about the impact of LHRH on melanoma cells, a fact reflected by the concluding comments from the authors that merely state that LHRH analogs "could be evaluated." This is a far cry from endorsing the treatment, *in vivo*, of GnRH-receptor positive melanoma cells.

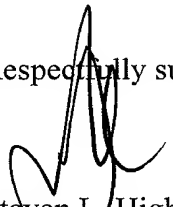
Next, applicants direct the examiner to claims 14 and 19, which recite that the treated tumors are GnRH-positive. The examiner has offered nothing to indicate that the SK-MEL-5 or SK-MEL-31 cells lines ever expressed GnRH receptor, or if they did, that they retained that receptor during the culturing prior to and including the experiments described in He *et al.* As such, applicants submit that the rejection falls for the simple reason that the reference fails to show each and every element of the invention as claimed.

Finally, applicants submit that even if a *prima facie* case of obviousness had been established by this reference, it would be more than adequately rebutted by the failure of those in the field to exploit or follow the observations of He *et al.* It is black letter law that secondary considerations such as long-felt need and failure of others are relevant to the issue of obviousness and ***must*** be considered in every case in which they are present. MPEP §2141. When evidence of any of these secondary considerations is submitted, the examiner ***must*** evaluate the evidence. Here, the simply fact some 14 years passed between the publication of the He *et al.* abstract and the filing of the present application ***must*** be accounted for, and there is no other reference cited by the examiner to indicate that anyone, much less one of skill in the art, placed any credence in the ambiguous data of He *et al.* This is an uncontroverted fact and must, according to the MPEP, be taken into consideration.

V. Conclusion

In light of the foregoing, applicants submit that all claims are in condition for allowance, and an early notification to that effect is earnestly solicited. Should the examiner have any questions regarding this submission, a telephone call to the undersigned is invited.

Respectfully submitted,



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